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PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of Delovitch, T. L.	)	Examiner: J. H. Roark
Serial No.: 09/341,407	)	Group Art Unit: 1644
Filed: October 12, 1999	)	
For: METHODS AND COMPOSITIONS FOR PREVENTING AUTOIMMUNE DISEASE	)	

Date: February 25, 2003

DECLARATION OF TERRY L. DELOVITCH

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Terry L. Delovitch, do hereby declare and say as follows:

1. I am presently Director and Scientist, Autoimmune Diabetes Group, John P. Robarts Research Institute, London, Ontario, Canada. I am also Professor, Department of Microbiology and Immunology, at the University of Western Ontario. A copy of my curriculum vitae is attached as Exhibit 1 to this Declaration.

2. I am the inventor named in the above-identified application and have read and understood the Office Action mailed on August 27, 2002.

3. The Examiner has rejected claims 1 to 6 and 8 to 9 under 35 U.S.C. 103(a) as unpatentabl over Rabinovitch (Diabetes (194), v. 43, pp. 613-621)

and L nschow et al. (Immunity (1996), v. 5, pp. 285-293) in view of either King et al. (Eur. J. Immunol., (1995), v. 25, pp. 587-595) or Webb et al. (Blood (1995), v. 86, pp. 3479-3486).

4. Rabinovitch (1994) discusses findings that both non-specific (e.g. using viral and bacterial materials) and specific stimulation of the immune system were able to reduce or prevent development of IDDM in NOD mice. They speculate that these interventions are effective by down-regulating Th1 T cells and up-regulating Th2 cells.

5. Subsequent to publication of the Rabinovitch paper, but before the priority date of the subject application, continuing studies of immune stimulation to prevent autoimmune diabetes gave results inconsistent with Rabinovitch's findings and revealed that predictions from Rabinovitch's findings did not hold true. For example, several clinical trials were conducted in humans using administration of the Bacillus Calmette-Guerin (BCG) vaccine to prevent development of diabetes (Shehadeh et al., (1994), Lancet, v. 343, pp. 706-707; Dahlquist et al., (1995), Diabetologia, v. 38, pp. 873-874): copies enclosed. These trials showed that this use of immune stimulation failed to prevent development of diabetes.

6. I believe that in view of these conflicting findings, one of skill in the art at the relevant time would not have had a reasonable expectation of success in treating or preventing IDDM by immunostimulation or by up-regulating the Th2 arm of the immune response.

7. The Lenschow reference presents a very confusing picture of the role of the CD28 pathway in the development of IDDM in NOD mice. The authors found that disruption of the CD28 pathway at 0 to 2 weeks of age gave an increased prevalence of IDDM in NOD mice, whereas disruption at 2 to 5 weeks had no

effect on disease incidence and disruption at 5 to 7 we ks gave suppression of the disease (page 290, column 2).

8. The authors also observed that CD28-negative NOD mice had T cells which responded poorly to many antigens but maintained a strong response to the IDDM-associated autoantigen, GAD. They note that "these results suggest that GAD-specific T cells can develop in the absence of CD28 co-stimulation."

9. In trying to explain the occurrence of GAD-sensitive T cells in CD28-negative mice, the authors also note that other co-stimulatory molecules which are present in these mice may substitute for CD28 in these mice (page 289, column 2).

10. Those of ordinary skill in the art were aware at the relevant time of alternative co-stimulating mechanisms such as CD43 (Sperling et al., (1995), J. Exp. Med., v. 182, pp. 139-146), CD40L (Greval etal., (1996), Science, v. 273, pp. 1864-1867), and LFA-1 (Wingrein et al., (1995), Crit. Rev. Immunol., v. 15, pp. 235-253); copies of these papers are submitted along with this Declaration. One of skill in the art would have been aware that these co-stimulating pathways were present and active in the CD28-negative NOD mice described in Lenschow's studies.

11. The Examiner concludes that, based on Lenschow's showing that inhibition of CD28 signalling during the first two weeks of life exacerbates IDDM, this would "suggest to one of ordinary skill in the art at the time of the invention was made that the opposite method of stimulating CD28 signalling during this critical window would have the opposite effect of inducing a TH2 response and protecting from development of diabetes."

12. I do not believe that one of skill in the art at that time would have drawn that conclusion regarding th effect of stimulating CD28 signalling in view of the

likelihood that other co-stimulatory molecules were compensating for lack of CD28 in these animals, as noted by Lenschow at al., and in view of the fact that the critical autoantigen-sensitive T cells were able to develop normally in the absence of CD28 signalling.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issued thereon.

Terry L. Delovitch

Date: July 8, 2003